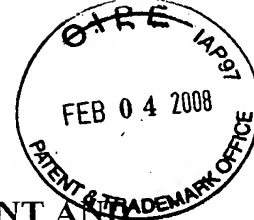


**MINISTRY OF PRODUCTIVE ACTIVITIES
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G2 DEPARTMENT**



*One 10.33 € revenue stamp and seal of the Ministry of Productive Activities.
Central Patent Office.*

**Certification of copy of documents relating to the patent application for:
Industrial Invention no. MI/2003/A/ 002286 of 24.11.2003**

It is hereby declared that the enclosed copy
corresponds to the documents as originally filed
with the patent application whose data are as
from the enclosed filing certificate

Rome, 21 December 2004

The Officer
Giampietro Carlotto
(Signature)

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CENTRAL PATENT OFFICE - ROME**

Space to be covered
with stamps
FORM A

APPLICATION FOR INDUSTRIAL INVENTION,
FILING MISSING DOCUMENTS, ADVANCED
AVAILABILITY TO THE PUBLIC

A. APPLICANT(S)

1) NAME **INDENA S.p.A.** J.S.
SEATING IN **Milano** CODE **0441780150**
2) NAME
SEATING IN CODE

B. APPLICANT'S REPRESENTATIVE AT THE CENTRAL PATENT OFFICE

SURNAME, NAME: **BIANCHETTI GIUSEPPE et al.** Taxpayer Identification Number:
NAME OF THE OFFICE: **BIANCHETTI BRACCO MINOJA S.r.l.**
STREET: **Via Rossini** N. **8** TOWN: **MILAN** ZIP CODE: **20122** PROV.: **MI**

C. ADDRESSEE'S ELECTIVE DOMICILE:

STREET: N. TOWN: ZIP CODE: PROV:

D. TITLE proposed class(sect/cl/scl): **[A61K]** group/sub-group: **[]**

"Compositions for the treatment of atopic dermatitis, skin allergic conditions and acne"

ADVANCED ACCESS TO THE PUBLIC: for months (at the most) YES ☐ NO ☒
IF REQUEST: DATE / / RECORD N. ☐

E. NAMED INVENTORS:

surname, name	surname, name
1) Bombardelli Ezio	3)
2)	4)

F. PRIORITY

COUNTRY OR ORGANIZATION	KIND OF PRIORITY	APPL.N.	FILING DATE	ENCL Y/M.
1)			/ /	
2)			/ /	

MISSING DOCUMENTS FILED: FILING DATE DOCUMENT N.

1)	/ /	
2)	/ /	

G. AUTHORIZED COLLECTING CENTER FOR MICROORGANISMS CULTURE

H. SPECIAL NOTES:

ENCLOSED DOCUMENTS:

	N. COPIES	
DOC. 1) [1] [PROV]		N.PAGES [11] abstract and main drawing, description and claims (1 copy compulsory)
DOC. 2) [0] [PROV]		N.SHEETS [] drawing (1 copy compulsory if OF DRAWING cited in the description)
DOC. 3) [0] [FOLLOWS]		power of attorney
DOC. 4) [0] [FOLLOWS]		designation of inventor
DOC. 5) [0] [FOLLOW]		priority documents with Italian translation

DOC. 6) [0] [FOLLOWS] authorization or assignment act
DOC. 7) [0] full name of the applicant

MISSING DOCUMENTS FILED:

DATE RECORD N.

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compare single priorities

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8. Payment receipts, Total amount Euros One hundred eighty-eight/51# compulsory

FILLED IN ON 24/11/2003

SIGNATURE OF THE APPLICANT(S)

CONTINUES YES/NO [NO]

Bianchetti Marina (signature)

CERTIFIED COPY OF THE PRESENT ACT IS REQUESTED YES/NO [YES]

PROVINCIAL OFFICE IND. TRADE HAND. OF MILAN CODE [15]

FILING CERTIFICATE: APPLICATION NUMBER MI2003A 002286 rec. A

The year **TWO THOUSAND AND THREE** this **TWENTY-FOURTH** day of the month of **NOVEMBER** the above mentioned applicant(s) has(have) produced to me the undersigned the present application, consisting of N. [00] additional sheets for the granting of the overmentioned patent.

**I. VARIOUS NOTES OF THE ATTESTING OFFICER THE REPRESENTATIVE,
EVEN THOUGH INFORMED OF THE CONTENT OF COMMUNICATION NO. 423 OF
03/01/2001, FILES THE DOCUMENT ASKING FOR AN EXTENSION OF TIME FOR
SUBMITTING THE POWER OF ATTORNEY**

THE PETITIONER SEAL OF THE OFFICE
(signature)

*Seal of the Ministry of
Productive Activities
One € 10.33 revenue stamp.*

THE ATTESTING OFFICER
M. CORTONESI
(signature)

ABSTRACT OF THE INVENTION WITH MAIN DRAWING, DESCRIPTION AND CLAIMS

Application N. MI2003A 002286
Patent N.

Filing date 24/11/2003
Granting date / /

D. TITLE

“Compositions for the treatment of atopic dermatitis, skin allergic conditions and acne”

L. ABSTRACT

The present invention relates to topical compositions containing:

- a) *Ginkgo biloba* terpenes;
 - b) floroglucinols pure or in mixture thereof, extracted from *Humulus lupulus*, *Hypericum* sp and *Mirtus* sp;
 - c) *Zanthoxylum bungeanum* or *Echinacea angustifolia* lipophilic extract;
- for the treatment of atopic dermatitis, skin allergic conditions and acne.

M. DRAWING

7158 M Description of the patent for industrial invention of title:
MAB/mc "COMPOSITIONS FOR THE TREATMENT OF ATOPIC
DERMATITIS, SKIN ALLERGIC CONDITIONS AND ACNE"

In the name of: INDENA S.p.A.

Seating in: Milano

5

* * *

The present invention relates to compositions containing vegetable extracts or purified and standardized fractions thereof, useful in the treatment of atopic dermatitis, skin allergic conditions and acne.

PRIOR ART

10 Atopic dermatites are characterized by persistent inflammatory conditions which may cause lacerations of the skin with possible infections. Inflammation is often accompanied by intense itching; the consequent scratching by the patient may further irritate the affected area.

15 Dermatites, which are also frequently referred to as eczema, are superficial skin inflammations, with acute or chronic course and variable clinical and histological manifestations, which affect an unnegligible percentage of population (2-3%).

20 The etiology of the various forms of dermatitis is still partly unclear, although the immune component is definitely one of the factors. The pathological manifestations are often alike, and are mainly characterized by the presence of papules, erythematous spots and vesicles, which can form plaques, edema, scaling-crusting lesions and the like. The most common dermatites comprise atopic dermatitis, contact allergies, contact dermatitis, stasis dermatitis, seborrheic dermatitis, lichen simplex and acne vulgaris.

25 The choice treatment consists in the use of corticosteroids, which involve well-known side effects (possible secondary infections, inefficacy after prolonged use, and the like).

DISCLOSURE OF THE INVENTION

It has now been found that compositions containing: a) an extract, fraction thereof or pure compound with inflammatory action; b) an extract, fraction thereof or pure compound, with antimicrobial and/or antifungal action; and c) an extract, 5 fraction thereof or pure compound, with anti-itching action exert immediate, beneficial effect to the patient and induce the fast remission of the pathological condition, even compared with known medicaments such as topical anti-inflammatories and steroids.

More precisely, the compositions of the invention comprise:

- 10 a) *Ginkgo biloba* terpenes;
- b) floroglucinols, either pure or in mixture thereof, extracted from *Humulus lupulus*, *Hypericum* sp and *Mirtus* sp;
- c) *Zanthoxylum bungeanum* or *Echinacea angustifolia* lipophilic extract.

According to the invention, *Ginkgo biloba* terpenes are present in the free 15 form or preferably in the form of complex with natural or synthetic phospholipids. "Ginkgo biloba terpenes" herein means the terpenes, either pure or in a mixture wherein the total triterpenes content ranges from 60 to 100%, preferably 90%, the bilobalide content ranges from 20 to 70%, preferably 45%, and ginkgolides A, B, C and J total content ranges from 25 to 75%, preferably 50%. *Ginkgo biloba* 20 terpenes, in addition to the antinflammatory action, also exert antiallergic action, as observed in a number of models both in animals and humans, thereby reducing one of the symptoms involved, which keep irritation and the continuous recidivation. This antiallergic action makes said terpenes particularly useful when an immune factor is involved in the etiology.

25 Floroglucinols, either pure or in a mixture thereof extracted from *Humulus lupulus*, *Hypericum* sp and *Mirtus* sp., are active against anaerobic bacteria such as *Propionibacterium acnis* and the like and on *Candida albicans* strains, at concentrations of 0.5-4 g/mL.

In particular, *Humulus lupulus* extracts are characterized by a floroglucinols content of 20 to 80%, preferably 60%. Among the extracts of *Hypericum* sp., particularly preferred is a *Hypericum perforatum* extract with a floroglucinols (adhyperforin/hyperforin) content ranging from 20 to 80%, preferably 60%.

5 Among the extracts of *Mirtus* sp, particularly preferred is an extract of *Mirtus communis* leaves prepared by extraction with carbon dioxide under pressure ranging from 235 to 260 bars, at a temperature ranging from 40 to 60°C, preferably a 45°C. The resulting extract usually contains a 35% concentration of mirtocumulone.

10 Compositions containing also natural compounds with estrogenic and/or antiandrogenic action proved particularly effective in the treatment of seborrheic dermatitis and acne. Therefore, according to a preferred aspect, the compositions of the present invention will contain, in addition to components a), b) and c) above, also natural compounds with estrogenic action, such as
15 ferutinine and/or extracts of various *Ferula* species, and/or natural compounds with antiandrogenic action, such as lauric acid.

The compositions of the invention containing a *Zanthoxylum bungeanum* or *Echinacea angustifolia* lipophilic extract enriched in isobutylamides, active as topical analgesics inhibiting the nervous conduction proved particularly effective
20 in the treatment of localized itching.

Therefore, according to a preferred aspect, the compositions of the present invention will contain, besides components a) b) and c) indicated above, *Zanthoxylum bungeanum* or *Echinacea angustifolia* lipophilic extract enriched in isobutylamides. The *Zanthoxylum* extract can be prepared for example as disclosed
25 in WO 00/02570, while the *Echinacea* extract can be prepared for example as disclosed in EP 0 464 298

According to a further preferred aspect, the compositions of the present invention will contain *Oenothera biennis* oil as lipophilic excipient.

The present invention, therefore, relates to topical compositions for the treatment of atopic dermatitis, skin allergic conditions and acne, containing the combinations described above. Said compositions will be prepared according to conventional methods well known in the pharmaceutical technique, such as those described in "Remington's Pharmaceutical Handbook", Mack Publishing Co., N.Y., USA, together with suitable excipients commonly used in the art.

The examples reported hereinbelow further illustrate the invention, without limiting its scope.

Example 1

Oil-in-water emulsion

	<i>Ginkgo biloba</i> terpenes in form of phospholipid complexes	0.5 g
	<i>Humulus lupulus</i> extract (60% in floroglucinols)	0.1 g
	<i>Zanthoxylum bungeanum</i> extract	0.05 g
	<i>Oenothera biennis</i> oil	5.0 g
15	Polyoxyethylene glycol-20 glyceryl stearate	10.0 g
	C ₁₀ -C ₁₈ triglycerides	10.0 g
	Glycerin	5.0 g
	Hydroxylated lanolin	0.5 g
	Hydroxyethyl cellulose	0.5 g
20	Methyl and propyl paraben	0.2 g
	Tocopherol	0.1 g
	Purified water	q.s. to 100.0 g

Example 2

Oil-in-water emulsion

25	<i>Ginkgo biloba</i> terpenes in form of phospholipid complexes	0.5 g
	<i>Mirtus communis</i> lipophilic extract (35% in mirtocumulone)	0.1 g
	<i>Zanthoxylum bungeanum</i> extract	0.05 g
	<i>Oenothera biennis</i> oil	5.0 g

	Stearic acid	10.0 g
	Mineral oil	6.0 g
	White petrolatum	6.0 g
	Sorbitan monostearate	2.0 g
5	Polyoxyethylene sorbitan monostearate	1.0 g
	Methyl and propyl paraben	0.2 g
	Purified water	q.s. to 100.0 g

Example 3

Cream

10	<i>Ginkgo biloba</i> terpenes in form of phospholipid complexes	0.5 g
	<i>Humulus lupulus</i> extract (60% in floroglucinols)	0.1 g
	<i>Echinacea angustifolia</i> extract	0.05 g
	<i>Oenothera biennis</i> oil	5.0 g
	Stearic acid	12.0 g
15	Glycerin	10.0 g
	Cetostearyl alcohol	2.0 g
	Potassium hydroxide	0.9 g
	Methyl and propyl paraben	0.2 g
	Purified water	q.s. to 100.0 g

Example 4

Cream

	<i>Ginkgo biloba</i> terpenes in form of phospholipid complexes	0.5 g
	<i>Hypericum perforatum</i> extract (60% in floroglucinols)	0.1 g
	<i>Echinacea angustifolia</i> extract	0.05 g
25	<i>Oenothera biennis</i> oil	5.0 g
	Stearic acid	12.0 g
	Glycerin	10.0 g
	Cetostearyl alcohol	2.0 g

Potassium hydroxide	0.9 g
Methyl and propyl paraben	0.2 g
Purified water	q.s. to 100.0 g

Example 5

5 Cream

	<i>Ginkgo biloba</i> terpenes in form of phospholipid complexes	0.5 g
	<i>Humulus lupulus</i> extract (60% in floroglucinols)	0.1 g
	<i>Zanthoxylum bungeanum</i> extract	0.05 g
	<i>Oenothera biennis</i> oil	5.0 g
10	Ferutinine	0.3 g
	Lauric acid	0.3 g
	Cetostearyl alcohol	20.0 g
	White petrolatum	15.0 g
	Propylene glycol	10.0 g
15	Sodium lauryl sulfate	1.0 g
	Methyl and propyl paraben	0.2 g
	Purified water	q.s. to 100.0 g

CLAIMS

1. Topical compositions for the treatment of atopic dermatitis, skin allergic conditions and acne, containing:
 - 5 a) *Ginkgo biloba* terpenes;
 - b) floroglucinols, either pure or in mixture thereof, extracted from *Humulus lupulus*, *Hypericum* sp and *Mirtus* sp;
 - c) *Zanthoxylum bungeanum* or *Echinacea angustifolia* lipophilic extract.
2. Compositions as claimed in claim 1, containing:
 - 10 a) 0.1 to 2% *Ginkgo biloba*;
 - b) 0.1 to 1% floroglucinols, either pure or in a mixture thereof, extracted from *Humulus lupulus*, *Hypericum* sp and *Mirtus* sp;
 - c) 0.01 to 0.5% of *Zanthoxylum bungeanum* or *Echinacea angustifolia* lipophilic extract.
- 15 3. Compositions as claimed in the above claims, wherein *Ginkgo biloba* terpenes are present in the free form.
4. Compositions as claimed in the above claims, wherein *Ginkgo biloba* terpenes are present in the form of complex with natural or synthetic phospholipids.
- 20 5. Compositions as claimed in claim 4, wherein the total triterpenes content ranges from 60 to 100%.
6. Compositions as claimed in claim 5, wherein the total triterpenes content is 90%.
7. Compositions as claimed in claim 4, wherein the bilobalide content
25 ranges from 20 to 70%.
8. Compositions as claimed in claim 7, wherein the bilobalide content is 45%.

9. Compositions as claimed in claim 4, wherein the total A, B, C and J ginkgolides content ranges from 25 to 75%.

10. Compositions as claimed in claim 9, wherein the total A, B, C and J ginkgolides content is 50%.

5 11. Compositions as claimed in claims 1-2, wherein the floroglucinols content of the *Humulus lupulus* extracts ranges from 20 to 80%.

12. Compositions as claimed in claim 11, wherein the floroglucinols content of the *Humulus lupulus* extracts is 60%.

10 13. Compositions as claimed in claims 1-2, wherein the *Hypericum* sp. extract is a *Hypericum perforatum* extract in which the floroglucinols content ranges from 20 to 80%.

14. Compositions as claimed in claim 13, wherein the floroglucinols content of the *Hypericum perforatum* extract is 60%.

15 15. Compositions as claimed in claims 1-2, wherein the extract of *Mirtus communis* leaves is prepared by extraction with carbon dioxide under conditions of pressure ranging from 235 to 260 bars and temperatures ranging from 40 to 60°C.

16. Compositions as claimed in claim 15, wherein the *Mirtus* sp. extract is an extract of *Mirtus communis* leaves with a mirtocumulone content of 35%.

20 17. Compositions as claimed in claims 1-2, wherein the *Zanthoxylum bungeanum* or *Echinacea angustifolia* lipophilic extract is enriched in isobutylamides.

18. Compositions as claimed in the above claims, further containing ferutinine.

25 19. Compositions as claimed in the above claims, further containing extracts of various *Ferula* species.

20. Compositions as claimed in the above claims, further containing lauric acid.

21. Compositions as claimed in the above claims, further containing *Oenothera biennis* oil as lipophilic excipient.

22. The use of a combination of:

a) *Ginkgo biloba* terpenes;

5 b) floroglucinols pure or in mixture thereof, extracted from *Humulus lupulus*, *Hypericum* sp and *Mirtus* sp;

c) *Zanthoxylum bungeanum* or *Echinacea angustifolia* lipophilic extract;

for the preparation of a medicament for the treatment of atopic dermatitis, skin allergic conditions and acne.

10 Milano, 24 November 2003

The Agent
Of Bianchetti Bracco Minoja S.r.l.
(Bianchetti Marina)
signature

STATEMENT

I, Catia Guerini Rocco, of Piazza Giovanni Paolo II, 16, 20089 Rozzano (MI), Italy, do hereby declare that I well understand the Italian and the English languages, and that the foregoing is a full, true and faithful translation carried out by me of Italian Patent Application No. MI 2003 A 002286 dated November 24, 2003.

Milan, October 15, 2007

Signature of the translator:

Catia Guerini Rocco